

## **REMARKS**

### **INTRODUCTORY MATTERS**

Claims 6-9 and 20-21 are pending in this application. Claims 1-5 and 10-19 are withdrawn. Following entry of this amendment, claims 6-9 and 20-21 will be pending.

### **THE AMENDMENTS TO THE SPECIFICATION**

Applicants have amended specification page 76 to insert the appropriate application numbers.

### **THE CLAIM AMENDMENTS**

Applicants have amended claim 6 to recite that the cleavable leader sequence is selected from the group consisting of a leader sequence derived from a second TGF- $\beta$  family protein, a metal-binding domain, a protein-binding domain, a ceramic-binding domain, a hydroxyapatite-binding domain and a collagen-binding domain. Support for amended claim 7 is provided in the specification at, *e.g.*, pages 20-21, and 77-82 and the claims as originally filed.

Applicants have amended claim 7 to recite a latent protein wherein a part of the leader sequence is cleaved. Support for this amendment is provide at, *e.g.*, specification page 21, lines 9-11.

Applicants have amended claims 9, 20 and 21 to improve their form.

None of the amendments introduces any new matter.

## **THE OBJECTIONS**

### **The Specification**

The Examiner has objected to specification page 76 stating that reference to the Attorney Docket No. should be replaced by the application number.

Applicants have amended specification page 76 as suggested by the Examiner, thus obviating the objection.

### **The Claims**

The Examiner has objected to claims 6-9 and 20 because they recite non-elected subject matter (TGF- $\beta$  family proteins) and has requested appropriate correction.

Applicants respectfully submit that no correction is necessary at this time. Applicants note that they elected the species OP-1 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Applicants submit that claims 6-9 and 20 are generic and encompass the elected species, OP-1. Accordingly, applicants request that the Examiner withdraw this objection.

## **THE REJECTIONS**

### **35 U.S.C. § 112, First Paragraph—Written Description**

1. The Examiner has rejected claims 6-9, 20 and 21 under 35 U.S.C. § 112, first paragraph for reciting new matter. The Examiner contends that claim 6 recites a limitation, "wherein said latent protein is a refolded protein," which introduces new matter. The Examiner states that the specification does not provide support for the limitation. The Examiner further states that by definition, a latent protein is an inactive

protein whereas a refolded protein is presumed to be an active protein. Applicants traverse.

Applicants respectfully submit that the specification does indeed provide adequate written description for the recitation of "wherein said latent protein is a refolded protein." Specifically, the specification at page 77, lines 8-14 discloses:

For example, H2440 is OP-1 with a hexa-his tag attached to its N-terminus as a binding domain for IMAC (immobilized metal affinity chromatography) resin. (Figure 7B). This protein has been purified over copper IMAC resin, initially in its unfolded state, in the presence of urea. After the purification of the unfolded protein on IMAC, followed by refolding, the successfully *refolded fraction is purified by RP-HPLC*. Such N-terminal fusion proteins *display little or no activity in a ROS assay*, but are *activated upon cleavage of the N-terminal* non-morphogen peptide to yield an active C-terminal morphogen domain. (Emphasis added.)

Therefore, contrary to the Examiner's assertion, a refolded protein as defined in the application is not active by definition. Applicants submit that the specification discloses a refolded latent protein which displays no activity but becomes activated upon cleavage of the leader sequence. Accordingly, applicants request that the Examiner withdraw this rejection.<sup>2</sup>

2. The Examiner has rejected claims 6-9, 20 and 21 under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner states that the claims encompass a genus of cleavable sequences operably linked to a genus of TGF- $\beta$  family

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<sup>2</sup> Applicants note that in the September 22, 2008 Advisory Action, the Examiner indicated that this response, which was previously submitted on August 21, 2008, overcame the rejection under 35 U.S.C. § 112, first paragraph for new matter.

protein C-terminal domains but that the claims do not require that the cleavable leader sequence possess any particular conserved structure nor other disclosed distinguishing feature.

Applicant traverses. However, solely to expedite prosecution of this application, applicant has amended claim 6 (and therefore claims dependent therefrom) to recite that the cleavable leader sequence is selected from the group consisting of a leader sequence derived from a second TGF- $\beta$  family protein, a metal-binding domain, a protein-binding domain, a ceramic-binding domain, a hydroxyapatite-binding domain and a collagen-binding domain. The specification at, e.g., pages 20-21, and 77-82 and the claims as originally filed provides adequate written description for claim 6 as amended. Accordingly, applicants request that the Examiner withdraw this written description rejection.

**35 U.S.C. § 112, Second Paragraph**

1. The Examiner has rejected claims 6-9, 20 and 21 under 35 U.S.C. § 112, second paragraph for being indefinite. Specifically, the Examiner contends that the recitation of "wherein said latent protein is a refolded protein" in claim 6 renders the claim indefinite. Citing to pages 68 and 79 of the specification, the Examiner contends that a latent form of a protein is inactive, whereas a correctly refolded protein presumably is active, and, therefore, the two limitations contradict each other.

Applicants traverse. First, applicants submit that nothing on pages 68 or 79 of the specification suggests that a refolded protein is necessarily active. Page 68 of

the specification states that there are assays to assess the activity of a refolded protein. That statement does not suggest that the refolded protein is necessarily active. Indeed, the disclosure at page 79 suggests that the latent protein is properly refolded and that the latent protein is delivered to a desired tissue locus and cleaved by, *e.g.*, naturally-occurring proteases at the target locus to produce an active morphogen (*see, e.g.*, page 79, lines 3-12). This disclosure, therefore indicates that the latent protein is properly refolded but is inactive due to the additional leader sequence which is cleaved at the tissue locus.

Second, as discussed above, the specification confirms this by the experimental results disclosed at page 77, lines 8-14 of the specification. Specifically, the specification discloses a modified OP-1 protein, H2440, which is a properly refolded but inactive latent protein, and is subsequently cleaved to release an active morphogen. Accordingly, applicants request that the Examiner withdraw this aspect of the indefiniteness rejection.<sup>3</sup>

2. The Examiner contends that claim 7 recites "wherein a tissue-targeting domain is embedded within said cleavable leader sequence" but that recitation contradicts the limitation "whereby cleavage of the leader sequence will not cleave said tissue-targeting domain from said C-terminal domain."

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<sup>3</sup> Applicants note that in the September 22, 2008 Advisory Action, the Examiner indicated that this response, which was previously submitted on August 21, 2008, overcame the rejection under 35 U.S.C. § 112, second paragraph.

Applicants traverse. Applicants respectfully submit that claim 7 is not unclear. The two portions of the claim identified by the Examiner are not contradictory. Notwithstanding, applicants have amended claim 7 to recite a latent protein wherein a part of the leader sequence is cleaved, thus rendering this aspect of the indefiniteness rejection moot.

For all the above reasons, applicants request that the Examiner withdraw the indefiniteness rejection.

### **CONCLUSION**

In view of the foregoing remarks and amendments, applicants request that the Examiner favorably reconsider this application and allow the amended claims pending therein. Should the Examiner feel that a telephone conference with applicants' representatives would assist the Examiner, she is invited to telephone the undersigned at any time.

Respectfully submitted,

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